REMARKS

Claims 1-21 are pending in the present application. Reconsideration of the application is respectfully requested in view of the following responsive remarks. For the Examiner's convenience and reference, Applicant's remarks are presented in the order in which the corresponding issues were raised in the Office Action.

In the office action of September 13, 2005, the following actions were taken:

(1) Claims 1-21 were rejected under 35 U.S.C. 112, second paragraph, as being indefinite; and

(2) Claims 1-21 were rejected under 35 U.S.C. 103(a) as being obvious in view of the combination of Grissom et al. US Pat. No. 6,797,521 (hereinafter "Grissom"), J. Org. Chem. (2002), Vol. 67, pages 1866-1872 (hereinafter "Toki"), Bioorganic & Medicianl Chemistry Letters (1998), Vol. 8, pages 3341-3346 (hereinafter "Dubowchik"), and US Pat. No. 5,574,018 (hereinafter "Habberfield").

It is respectfully submitted that the presently pending claims be examined and allowed. Applicants submit that each and every amendment herein, and throughout the prosecution of the present application is fully supported by the specification as originally filed, and that no new matter has been added.

Rejections under 35 U.S.C. § 112, second paragraph

The Examiner has rejected claims 1-21 as being indefinite because the components of the anti-tumor drug and cobalamin conjugate are only described in functional terms. The Applicants respectfully submit that these claims are not indefinite for the reasons set forth below, and that the rejection should be withdrawn.

The pending claims are not indefinite when analyzed in light of the Applicants' specification, the prior art, and the knowledge of the skilled artisan. According to the MPEP:

> Definiteness of claim language must be analyzed, not in a vacuum, but in light of:
>
> (A) The content of the particular application disclosure;
> (B) The teachings of the prior art; and
> (C) The claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made.

In the Applicants' specification, the components of the anti-tumor drug and cobalamin conjugate are described and defined in more detail. For example, on page 13 of the specification, the Applicants provide a definition for cobalamin and a list of compounds that are included by the term cobalamin. The conjugate unit, including at least a "linker," is described in detail on pages 15 through 26 of the Applicants' specification. Page 20 of the specification depicts a table listing several groups that could be used as linkers along with the corresponding enzymes that would provide the desired cleavage of the linker. The term anti-tumor drug is described on pages 31 through 35. The Applicants define the term anti-tumor drug and also list compounds that are exemplary of anti-tumor drugs that are suitable for use with the invention. Therefore, one of ordinary skill in the pertinent art would be apprised of the meets and bounds of the components of the anti-tumor drug and cobalamin conjugate. Accordingly, the Applicants respectfully request that the Examiner's rejection of claims 1-21 for indefiniteness be withdrawn.

Claims 8 and 9 have been amended in response to the Examiner's rejections of these claims. Applicants respectfully request that the Examiner's rejection of claims 8 and 9 for indefiniteness be withdrawn after consideration of these amendments.

Rejection Under 35 U.S.C. § 103

The Examiner has rejected claims 1-21 as being obvious in view of the combination of Grissom, Toki, Dubowchik, and Habberfield. The Applicant respectfully submits that these claims are patentable over the cited references for the reasons set forth below, and that the rejection should be withdrawn. The following discussion of the cited references is currently focused on the combination's lack of each and every element of the present invention, the lack of motivation to combine or modify the references, and the lack of a reasonable expectation of success in combining the references. Therefore, the following discussion of applicable case law is considered an important background for the Examiner to keep in mind during this discussion.

Before specifically discussing the obviousness rejections herein, it is thought proper to briefly state what is required to sustain such a rejection. The issue under § 103 is whether the PTO has stated a case of *prima facie* obviousness. Additionally, the Examiner's suggested combination must also have a reasonable expectation of success, from the perspective of one skilled in the art, at the time the invention was made. Further, the Examiner must establish some motivation or suggestion to combine and/or modify the references, where the motivation must arise from the references themselves, or the knowledge generally available to one of ordinary skill in the art. The Applicant respectfully asserts the Examiner has not satisfied the requirements for establishing a case of *prima facie* obviousness in any of the § 103(a) rejections. The combination proposed by the Examiner would not make successful practice of the claimed invention obvious to one of ordinary skill in the art. Accordingly, Applicant contends that the Examiner has failed to meet its burden of establishing a *prima facie* case of obviousness.

The Combination of Grissom, Toki, Dubowchik, and Habberfield

The Examiner has rejected claims 1-21 as being obvious over the combination of Grissom, Toki, Dubowchik, and Habberfield.

Lack of Each and Every Element

The combined references do not teach or suggest all the claim limitations of the instant application. According to the MPEP § 2142, the Examiner has the burden and must establish a case of *prima facie* obviousness by showing the prior art reference, or references combined, teach or suggest all the claim limitations in the instant application. The chemical structure of claims 1 and 7 (the independent claims) require cobalamin to be covalently bound via its 5'OH of the ribose ring to either an optional spacer or to an intracellular enzyme cleavable linker. The linker is then covalently bound to either an optional spacer or to an anti-tumor drug. Thus, the present invention requires a linker that is reactive to both cobalamin at the 5'OH group and to an anti-tumor drug – or spacer there between. In other words, multiple points of attachment to the linker are required. A peptide or non-peptide linker that can join two moieties together must be selected, and then the proper chemical reactions for attaching the peptide at two (2) locations, one side to a cobalamin and one side to an anti-tumor drug, be performed.

The Grissom patent relates to fluorescent compounds that are covalently linked to a cobalamin and used as diagnostic and prognostic markers. The markers can distinguish cancer cells and tissues from healthy cells and tissues and also determine if an individual will respond to chemotherapy treatments using cobalamin-therapeutic bioconjugates. Grissom does teach a doxorubicin-cobalamin conjugate synthesized as a potential chemotherapeutic compound; however, as the Examiner points out, Grissom is silent on the chemical structure of the doxorubicin-cobalamin conjugate. Grissom also fails to disclose the possibility of an enzyme cleavable linker. Additionally, Grissom teaches away from the instant invention. Grissom teaches that it is preferred to covalently link a fluorescent compound to the corrin ring or the ribose moiety of the cobalamin. Column 2, lines 35-37. The instant claims requires a linker or optional spacer to be covalently bound to cobalamin by the 5'OH group of the ribose moiety, which would preclude covalently linking a fluorescent compound to the ribose moiety.

Toki does not cure the defects of Grissom. Toki teaches a general method of activating anticancer drugs using proteases within solid tumors. Toki describes anticancer drugs that can be appended to a peptide, decreasing the toxicity of the anticancer drugs. Although Toki teaches the use of spacers between the peptide and

the anticancer drug, the peptide is not used as a linker to another moiety as required by the present claims. Once the drug-peptide complex enters a tumor cell, the cell's enzymes cleave the peptide and release the drug from the peptide. However, the instant invention requires a peptide (or non-peptide) linker between the antitumor drug and a cobalamin moiety. (Page 15 and page 20) Toki does not teach the use of peptides as linkers to another moiety, and does not teach the use of non-peptides at all. Toki also fails to include cobalamin, much less the required limitation of having a linker or spacer covalently bonded to the 5'-OH group of the ribose moiety of cobalamin.

Dubowchik is very similar to Toki because it also describes a drug stabilized by a peptide. Dubowchik teaches stabilizing doxorubicin, an anti-tumor drug, with an enzyme-cleavable peptide and a self-immolative PABC spacer. The peptide can be cleaved by cathepsin B and the drug released, however the peptide-drug compounds are very stable in human plasma. Dubowchik's focus is on studying and describing the structural requirements of the enzyme-cleavable peptides that can be used efficiently to release the doxorubicin. Although Dubowchik describes its peptides as "linkers," Dubowchik does not teach the use of the peptides as linkers in the manner required by the claims of the instant invention, where a peptide (or nonpeptide) is a linker between a drug and a cobalamin. Additionally, Dubowchik fails to include any suggestion or reason for using anything in addition to the peptide and the self-immolative spacer, such as a cobalamin. Because the use of a cobalamin is not suggested by Dubowchik, the reference is also lacking the required limitation of having a linker or spacer covalently bound to the 5'OH group of the ribose moiety of the cobalamin.

Habberfield teaches the use of biologically active conjugates of vitamin B_{12} (a cobalamin) and a therapeutically useful protein covalently linked via the 5'OH group of the ribose moiety of vitamin B_{12}. Habberfield explains "[a]ny polypeptide which is a therapeutically useful protein and is capable of covalent binding to the VB_{12} compound can be utilized in the practice of this invention." Column 5, line 10-12. Habberfield does not envision this polypeptide to act as a linker, but as the actual therapeutic substance. The purpose of attaching the vitamin B_{12} to substances such as drugs, hormones, antigenic material, and the like, is to transport the substances from the intestinal lumen into circulatory blood. The therapeutically useful protein is

linked directly to the vitamin B12 and does not suggest that the therapeutically useful protein could be linked to an anti-tumor drug. Thus, Habberfield does not include any teaching of a linker attached to the 5'OH group of a cobalamin. Additionally, there is no mention of using anti-tumor drugs in combination with this invention. The fact that Habberfield recognizes that therapeutically useful peptides can bind to the 5'OH group of the ribose moiety of vitamin B12 does not suggest that that the very peptide that binds the 5'OH can also be bound to a anti-tumor drug at another site. There is no suggestion that the invention be practiced in connection with a linker (which must be reactive to both cobalamin at the 5'OH group and to an anti-tumor drug – or spacer there between). In other words, none of the references teach or suggest multiple points of attachment with respect to the peptide. Thus, a *prima facie* case of obviousness cannot be maintained by the combination put forth by the Examiner.

Even if combined as proposed, one skilled in the art would still have to modify the four reference combination. According to the present invention, peptide and non-peptide linkers must be specifically selected for their ability to link two moieties together, which is not taught in any of the references. After suitable linkers are selected, the proper chemical reactions and conditions must be selected for attaching the linker at two (2) locations, one side to cobalamin and one side to an anti-tumor drug. In the chemical arts, this is not typically a simple proposition. In short, the combination of references set forth by the Examiner still do not teach or suggest using linkers for their characteristic of having multiple points of attachment, and further, none of the references address the complexities created by this requirement. Therefore, each and every element of the claimed invention is not present in the combination of references suggested by the Examiner.

No Motivation to Combine References

Even if the Examiner maintains that each and every element of the present invention is found in the suggested combination of references, there is no motivation to combine the references as suggested by the Examiner. The Federal Circuit explained,

> [V]irtually all [inventions] are combinations of old elements. Therefore, an examiner may often find every element of a claimed invention in the prior art. If identification of each claimed element in the prior art were sufficient to

> negate patentability, very few patents would ever issue. Furthermore, rejecting patents solely by finding prior art corollaries for the claimed elements would permit an examiner to use the claimed invention itself as a blueprint for piecing together elements in the prior art to defeat the patentability of the claimed invention.
>
> . . . To counter this potential weakness in the obviousness construct, the suggestion to combine requirement stands as a critical safeguard against hindsight analysis and rote application of the legal test for obviousness.

In re Rouffet, 149 F.3d 1350, 1357-58, 47 U.S.P.Q.2d 1453, 1457 (Fed. Cir. 1998) (internal citations omitted). "For a chemical compound, a prima facie case of obviousness requires 'structual similarity between claimed and prior art subject matter . . . where the prior art gives reason or motivation to make the claimed compositions.'" *Yamanouchi Pharmaceutical Co. Ltd. v. Marsam Pharmaceuticals, Inc.*, 231 F. 3d 1339, 1343, 56 U.S.P.Q.2d 1641 (Fed. Cir. 2000) (internal citations omitted).

Although the Examiner's combination of references includes a cobalamin attached to a peptide, a cobalamin attached to an anti-tumor drug, and an anti-tumor drug attached to a peptide, the combination of references does not suggest any reason for combining the three compounds into one. Grissom offers no suggestion of how the cobalamin should be attached to an anti-tumor drug, much less any reason for including a linker between the cobalamin and the anti-tumor drug. Toki and Dubowchik suggest that certain peptides combined with self-immolative spacers can stabilize certain anti-tumor drugs and offer scientific evidence of doing it successfully. Thus, there is no suggestion or motivation for adding an additional compound, such as a cobalamin, found in Toki or Dubowchik. In Habberfield, the peptide itself is the therapeutic substance. Thus, there is no suggestion or motivation provided by Habberfield for including an anti-tumor drug with the therapeutically useful protein. In short, the Examiner's combination of four references fits the description offered by the Federal Circuit of using the claimed invention itself as a blueprint for piecing together elements in the prior art. There is no suggestion that the invention be practiced in connection with a linker (which must be reactive to both cobalamin at the 5'OH group and to an anti-tumor drug – or spacer there between). In other words, none of the references teach or suggest multiple points of attachment

with respect to the peptide. Thus, a *prima facie* case of obviousness cannot be maintained by the combination put forth by the Examiner.

As mentioned above, even if combined as proposed, one skilled in the art would still have to further modify the combination. According to the present invention, peptide and non-peptide linkers must be specifically selected for their ability to link two moieties together. After suitable linkers are selected, the proper chemical reactions and conditions must be selected for attaching the linker at two (2) locations, one side to cobalamin and one side to an anti-tumor drug. The references suggested by the Examiner do not teach or suggest using linkers with multiple points of attachment and they do not address the complexities created by such a requirement. Therefore, each and every element of the claimed invention is not present in the combination of references suggested by the Examiner.

Reasonable Expectation of Success

The Examiner's suggested combination further fails to meet the requirements for establishing a prima facie case of obviousness because there is no reasonable expectation of successfully combining the elements to form the present invention. The Examiner must show that a person of ordinary skill in the art would have a reasonable expectation of success to establish a prima facie case of obviousness. *See Noelle v. Lederman*, 355 F.3d 1343, 1352 (Fed. Cir. 2004) (explaining that the reasonable expectation of success must be founded in the prior art).

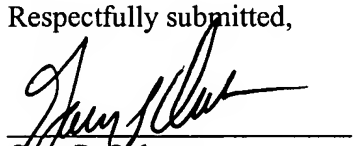
According to the present invention, peptide and non-peptide linkers must be specifically selected for their ability to link two moieties together. After suitable linkers are selected, the proper chemical reactions and conditions must be selected through trial and error. Just because the combination suggested by an Examiner might be obvious to try, does not mean that there is a reasonable expectation that the combination would be successful. The references suggested by the Examiner fail to teach or suggest using linkers with multiple points of attachment and they do not address the complexities created by such a requirement. Therefore, there is no reasonable expectation that the combination of references as suggested by the examiner would be successful if carried out by one of ordinary skill in the art.

In view of the foregoing, Applicants believe that claims 1-21 present allowable subject matter and allowance is respectfully requested. If any impediment to the allowance of these claims remains after consideration of the above remarks, and such impediment could be removed during a telephone interview, the Examiner is invited to telephone the undersigned attorney at (801) 566-6633 so that such issues may be resolved as expeditiously as possible.

Please charge any additional fees except for Issue Fee or credit any overpayment to Deposit Account No. 20-0100.

Dated this 7th day of July, 2006.

Respectfully submitted,



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